tributed, on the basis of molecular orbital calculations, to $d\pi$–$p\pi$ bonding between the double bond and silicon.[30] However, this requires the planar trans conformation **4** (X = $Si(CH_3)_3$) which on the basis of arguments presented in this paper would not be highly populated if at all. Thus, the effects of conformation and σ–π delocalization of the double bond must be considered to fully explain the reasons for extended conjugation in these allyl organometallic compounds.

In summary, EH calculations suggest that allylmercuric derivatives should exist principally in a conformation intermediate between the two gauche forms **2** and **3** due in part to delocalization of the double bond. The activation energy for electrophilic addition to allyl mercurials is markedly reduced by σ–π stabilization of the neighboring cationic center as depicted in the planar configuration **7**. These results further support the existence of mercurinium cations which may be formed either by the electrophilic addition of Hg^{2+} to an olefin or by protolysis of σ-bonded allylic mercurials. Although mercurinium ions have been postulated on the basis of experimental and theoretical data, they have only recently been observed by nmr spectroscopy.[31] In view of the current interest in the concept of a three-atom triangle which includes a metal atom that has also been proposed in metal–metal exchange processes,[32] we hope that molecular orbital calculations of this type will help to provide a unifying theory describing the nature of these cyclic intermediates.

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Oxidative Cleavage of Hydroquinone Ethers with Argentic Oxide

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Abstract: The scope and mechanism of argentic oxide (AgO)–oxidative ether cleavage of both naphtho- and benzohydroquinone dimethyl ethers have been investigated. The reaction is accomplished most efficiently in dilute, aqueous, acidified dioxane solution, the *p*-quinones being formed immediately at room temperature in high yield. Reaction in an $H_2{}^{18}O$ enriched milieu provides proof that aryl–oxygen bond cleavage is involved during the oxidation. Oxidation-sensitive functions such as alcohols, aldehydes, ketones, and olefins survive the reaction intact, illustrating the selectivity obtainable. *o*-Quinones also can be formed in moderate yield from 4,5-disubstituted 1,2-dimethoxy (or methylenedioxy)benzenes. In addition, where possible, polymethoxylated nuclei are demethylated to yield both *o*- and *p*-quinones. The application of these results to protection–deprotection of quinones as well as to demethylation of natural products is discussed.

The problem of demethylation of aryloxy methyl ethers ($ArOCH_3$) is a general one in synthetic organic chemistry. Classically these ethers have been cleaved only with strong, sometimes aprotic, acids and more recently under equally drastic nucleophilic conditions.[1] As a result the use of methyl ether protecting groups is limited by the stability of the nucleus and its substituents to the vigorous conditions required for their removal and some natural products containing methoxyl groups are demethylated nondestructively only with difficulty. However, if the molecule contains ortho or para methoxyl groups, then alternative oxidative demethylation pertains. The resulting quinone can be reduced quantitatively to the hydroquinone or catechol if simple demethylation were the desired overall reaction. Protection of a quinone as the dimethyl ether of the hydroquinone has considerable advantage for synthetic quinone chemistry in that it allows manipulation of the molecule under strongly anionic conditions which are precluded by the use of simple hydroquinone esters.[2] The small steric bulk and general unreactivity of the methoxyl group makes it an ideal blocking group and facilitates nucleophilic condensation reactions of the type already reported.[3] Since many quinones of biological interest bear acid-sensitive isoprenoid side chains, demethylation requires mildly acidic conditions, thus eliminating the most effective acidic reagents. In addition we have observed that hydroquinone dimethyl ethers are resistant to alkaline cleavage of the type which has been effective with simple anisoles.[4] Thus, a successful method of oxidative demethylation would be particularly attractive.

As reviewed in 1969,[5] oxidative demethylation of

(1) (a) J. W. Wildes, N. H. Martin, C. G. Pitt, and M. E. Wall, *J. Org. Chem.*, **36**, 721 (1971), and references therein; (b) F. G. Mann and M. J. Pragnell, *J. Chem. Soc.*, 4120 (1965); (c) I. M. Lockhart and N. E. Webb, *Chem. Ind. (London)*, 1230 (1970); (d) J. A. Zoltewicz and A. A. Sale, *J. Org. Chem.*, **35**, 3462 (1970).

(2) Hydroquinones esterified with a bulky group such as pivaloyl have proved inert during Wittig reaction; see W. E. Bondinell, S. J. DiMari, B. Frydman, K. Matsumoto, and H. Rapoport, *ibid.*, **33**, 4351 (1968).

(3) W. E. Bondinell, C. D. Snyder, and H. Rapoport, *J. Amer. Chem. Soc.*, **91**, 6889 (1969); *J. Org. Chem.*, **36**, 3951 (1971).

(4) *E.g.*, we have found that 2,3-dimethyl-1,4-dimethoxynaphthalene is not demethylated by aqueous methylamine at 185° (ref 1c).

(5) O. C. Musgrave, *Chem. Rev.*, **69**, 499 (1969).

Table I. Oxidation of Various Aryloxy Ether Substrates with AgO[a]

Substrate	Product	Yield,[b] %
Naphthalene	Naphthoquinone	
1,4-dimethoxy-	1,4-	92
2,3-dimethyl-1,4-dimethoxy-	2,3-dimethyl-1,4-	90
	2,3-dimethyl-1,4-	92[c]
	2,3-dimethyl-1,4-	73[d]
2-methyl-3-(3-methyl-2-butenyl)-1,4-dimethoxy-	2-methyl-3-(3-methyl-2-butenyl)-1,4-	92
2-methyl-3-oxymethyl-1,4-dimethoxy-	2-methyl-3-oxymethyl-1,4-	89
2-methyl-3-formyl-1,4-dimethoxy-	2-methyl-3-formyl-1,4-	80
2-methyl-1,3,4-trimethoxy-	2-methoxy-3-methyl-1,4-	40
	4-methoxy-3-methyl-1,2-	50
Benzene	Benzoquinone	
1,4-dimethoxy-	1,4-	78
4,5-dimethyl-1,2-dimethoxy-	4,5-dimethyl-1,2-	55
4,5-dimethyl-1,2-methylenedioxy-	4,5-dimethyl-1,2-	60
1-methyl-2,3,4,5-tetramethoxy-	2,3-dimethoxy-5-methyl-1,4-	64

[a] The reaction mixture contains 1 mmol of substrate/10 ml of dioxane; AgO (4 mmol) and then nitric acid (6 mmol) are added to initiate the oxidation. [b] Yield is determined by quantitative gc, extinction coefficient, or isolation; details are given in the Experimental Section for each reaction. [c] Using perchloric acid. [d] Using phosphoric acid.

hydroquinone dimethyl ethers is most commonly observed upon exposure to concentrated nitric acid, and occurs either in addition to or instead of nitration. Peroxy acids also under certain conditions will hydroxylate a 1,2- or 1,4-dimethoxy nucleus, resulting in oxidative demethylation, but this is invariably a low-yield side reaction with respect to other hydroxylations. Inorganic oxidants such as cerium (4+), permanganate, or chromium (3+) can accomplish oxidative demethylation although again side reactions such as oxidative dimerization in the case of cerium (4+) frequently prevail.[5]

With quinones and other molecules of biological interest oxidation conditions must be specific enough to allow survival of other oxidation-sensitive structural features while permitting demethylation. One reagent, which from recent studies appears to achieve selective oxidation of organic substrates, is AgO in acidic milieu.[6] Since studies of selective oxidation with this reagent lead to the observation that it also effected oxidative demethylation in good yield,[3] further work was pursued to establish the scope and mechanism of this interesting new reaction with emphasis upon application to quinone and other natural product chemistry. The results are reported herein.

Discussion

If one mixes a hydroquinone dimethyl ether such as 2,3-dimethyl-1,4-dimethoxynaphthalene with argentic oxide in aqueous dioxane solution, no reaction is observed even at elevated temperatures until a mineral acid is added. Then immediately even at 0°, quinone formation occurs. The oxidant must be present in fourfold molar excess for quantitative conversions although stoichiometrically only 2 mol is required, the excess apparently being consumed in oxidation of the methoxyl fragments and/or solvent. Also, the acid must be in molar excess relative to oxidant and must contain enough water to prevent, if possible, silver salt precipitation which by nucleation on unconsumed argentic oxide retards further oxidation. For this reason, acids which form water-soluble silver salts such as nitric and perchloric are most efficient (Table I).

In order to determine the stability of various functional groups to the oxidation conditions several 2,3-disubstituted 1,4-dimethoxynaphthalenes were synthesized and oxidized to the corresponding naphthoquinones. As can be seen from Table I, the peripheral groups tested survived intact. No allylic oxidation or epoxidation could be detected upon oxidation of the dimethyl ether of menaquinol-1 [2-methyl-3-(3-methyl-2-butenyl)-1,4-dimethoxynaphthalene], a relevant model for isoprenoid quinones. Further, the acid conditions employed are mild enough to avoid cyclizations of the side chain observed under more vigorous conditions.[7]

2-Methyl-3-oxymethyl-1,4-naphthoquinone is obtained without a trace of further oxidation at the 3 position in spite of the facility with which AgO will oxidize benzyl alcohols to the corresponding aldehydes.[6] The rate difference between the two modes of oxidation apparently is sufficient to allow only demethylation to be observed; the product quinone, being substantially more resistant to further oxidation by AgO than the fully aromatic starting material, is thus recovered intact.

Similarly, the unusually substituted quinone, 2-methyl-3-formyl-1,4-naphthoquinone, is obtained without further oxidation in contradistinction to an attempted preparation of the analogous compound by oxidative demethylation of 2-formyl-3,5,6-trimethyl-1,4-dimethoxybenzene with concentrated nitric acid in which oxidative decarboxylation of the formyl group followed by nitration is observed.[8] Finally, when 2,3 disubstitution is not present, 1,4-naphthoquinone is still obtained in 92% yield, indicating that aromatic hydroxylation is not an important side reaction, again probably reflective of the sensitivity of the 1,4-dimethoxy arrangement to oxidative demethylation.

The application of this method to the generation of benzoquinones was tested on 1,4-dimethoxybenzene itself, with *p*-benzoquinone resulting in 78% yield. Presumably substituted benzoquinones would be obtained at least as efficiently so that a methylation protection–deprotection scheme is applicable to the

(6) L. Syper, *Tetrahedron Lett.*, 4193 (1967).

(7) C. H. Shunk, N. R. Trenner, C. H. Hoffman, D. E. Wolf, and K. Folkers, *Biochem. Biophys. Res. Commun.*, **2**, 427 (1960).

(8) L. I. Smith and F. J. Dobrovolny, *J. Amer. Chem. Soc.*, **48**, 1693 (1926).

plastoquinone and tocopherolquinone, as well as menaquinone, series.

Mechanistically, this oxidation is most conveniently investigated by the use of ^{18}O in order to determine the carbon–oxygen bonds cleaved during the reaction. One can envisage four different mechanisms for insertion of oxygen (Scheme I); that is, oxidation–hydration can take place at either the methyl carbon (a), the aromatic carbon (b, c), or in a hybrid mechanism at both (d). Whether oxidation occurs *via* an oxidized water species, *i.e.* [OH^+] generated freely or in a concerted manner ($2Ag^{2+} + H_2O \rightarrow 2Ag^+ + H^+ + OH^+$), oxidation of a hydrated aromatic species, or hydration of an oxidized aromatic species cannot be directly investigated. However the apparent lack of hydroxylation side reactions seems to rule out the [OH^+] species at least in the classical sense. The silver species accepting electrons is presumed to be Ag^{2+} although a two-electron shift reducing Ag^{3+} is possible since a $2Ag^{2+} \rightleftarrows Ag^{3+} + Ag^+$ disproportionation reaction is thought to pertain to some extent in aqueous acidic solution.[9]

$H_2{}^{18}O$-labeled 85% phosphoric acid was conveniently prepared by hydration of phosphorus pentoxide with ^{18}O-enriched water. In this manner some of the label was introduced into the phosphoric acid but subsequent loss of label from the water by exchange with the oxygens of phosphoric acid is reported to be negligible.[10] 2,3-Dimethyl-1,4-dimethoxynaphthalene was then oxidized in the ^{18}O-enriched milieu and compared to a control sample of 2,3-dimethyl-1,4-naphthoquinone exposed to the same conditions. As can be seen in Table II, quinone produced in the presence of $H_2{}^{18}O$

Table II. AgO Oxidative Demethylation Study in the Presence of $H_2{}^{18}O$ and H_3PO_4 (1.70% ^{18}O[a])

Substrate	^{18}O, %[b]	Product	^{18}O, %[b]
2,3-Dimethyl-1,4-dimethoxynaphthalene	0.28	2,3-Dimethyl-1,4-naphthoquinone	1.65
2,3-Dimethyl-1,4-naphthoquinone	0.28	2,3-Dimethyl-1,4-naphthoquinone	0.28

[a] ^{18}O content determined directly by mass spectrometry. [b] ^{18}O content determined by pyrolysis to carbon monoxide and then mass spectrometry (C. D. Snyder and H. Rapoport, *Biochemistry*, **7**, 2318 (1968)).

became completely labeled whereas no incorporation was detectable in the control quinone; therefore, the mechanism for this oxidation must be type b or c. It should also be noted that oxidative attack of water at the aromatic carbons is observed in an example in which hindrance at those carbons is maximal.[11] Such a mechanism, however, is not completely without precedent since several monomethyl- and monophosphorylhydroquinones give almost total aryl–oxygen bond cleavage upon oxidation.[12]

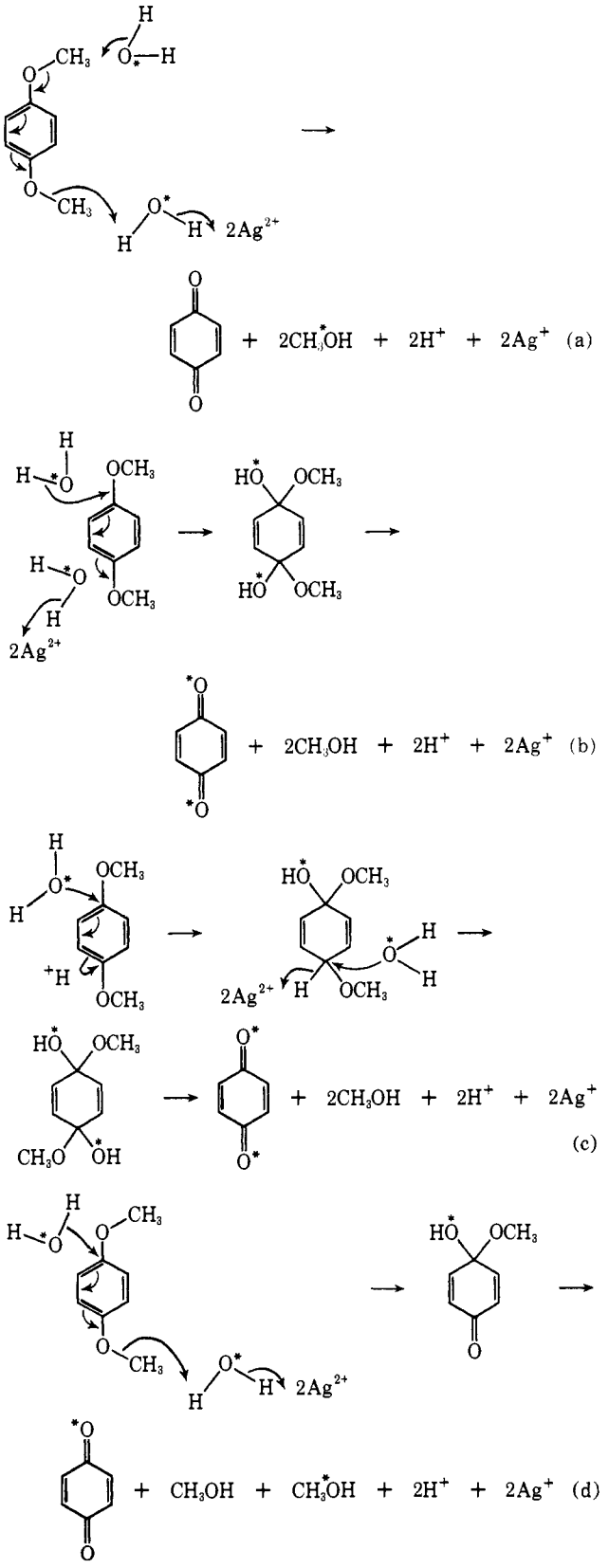
(9) J. A. McMillan, *Chem. Rev.*, **62**, 65 (1962).

(10) C. A. Bunton, D. R. Llewellyn, C. A. Vernon, and V. A. Welch, *J. Chem. Soc.*, 1636 (1961).

(11) A measure of the hindrance involved can be obtained from a study of the acid-catalyzed carbonyl–water exchange rates of 2,3-dimethyl-1,4-naphthoquinone and 1,4-naphthoquinone in which exchange of the unhindered quinone oxygens was favored by a factor of 50 (see Snyder and Rapoport, Table II, footnote *b*).

(12) (a) W. Durckheimer and L. A. Cohen, *Biochemistry*, **3**, 1948 (1964); (b) A. Lapidot and D. Samuel, *Biochem. Biophys. Acta*, **65**, 164 (1962); (c) E. Adler, I. Falkehag, and B. Smith, *Acta Chem. Scand.*, **16**, 529 (1962); (d) H. Mayer, W. Vetter, J. Metzger, R. Ruegg, and O. Isler, *Helv. Chim. Acta*, **50**, 1168 (1967).

Scheme I. Four Possible Modes of Carbon–Oxygen Bond Cleavage during AgO Oxidative Demethylation



Since many natural products contain methylenedioxy or ortho dimethoxy substituents, extension of oxidative ether cleavage to this class of compounds seemed particularly relevant. 4,5-Dimethyl-1,2-benzo-

quinone was chosen as a model product, the 4,5 disubstitution reflecting a common biological pattern and one which should be stable to the reaction conditions. *o*-Quinones are fairly stable to addition in mildly acidic aqueous medium if reactive nucleophiles are not present[13] but, on the other hand, are easily further oxidized. Fortunately, 4,5-dimethyl-1,2-benzoquinone exhibited a decomposition rate under the reaction conditions of only 1%/min, as determined by the decrease in visible extinction. Since the demethylation reaction is generally complete in less than 1 min such a rate of oxidative destruction was acceptable.

Therefore, 4,5-dimethyl-1,2-dimethoxybenzene, prepared by methylation of the catechol with dimethyl sulfate, was oxidized with argentic oxide, removing aliquots periodically for spectrophotometric analysis. Because of the difficulties involved in quantitative recovery of *o*-quinones, the yield was determined most accurately by extinction coefficients utilizing the 398- and 555-nm absorptions which are distinctive of the *o*-benzoquinone chromophore.[14] Pure product obtained by recrystallization and compared with authentic quinone confirmed the structural and yield assignment. Thus, from Table I, 4,5-dimethyl-1,2-benzoquinone is formed in 55% yield after a 1-min exposure at 0° to AgO.

Since oxidation involves attack of water at the aryl carbon the reaction should be moderately insensitive to the nature of the ether component except as it influences steric approach to the nucleus. Therefore, cleavage of a methylenedioxy ether should be as facile as oxidative demethylation, the alkoxy fragment simply being expelled as formaldehyde instead of methanol. To test this hypothesis, 4,5-dimethyl-1,2-methylenedioxybenzene was synthesized by methylenation of the corresponding catechol with methylene bromide in DMF–K_2CO_3,[15] and the ether so obtained was subjected to AgO oxidation at 0° to yield the *o*-quinone. From the nmr spectrum, signals at δ 2.15, a doublet (J = 1 Hz) corresponding to the 4,5-dimethyl substituents, and at 6.22, a broad singlet containing the 2,6-aromatic protons, are singular and diagnostic, confirming a 60% yield as estimated by extinction coefficient.

If 4,5 disubstitution is removed, however, other reactions prevail since both 1,2-dimethoxynaphthalene, in which a para position is open, and veratrole, a totally unsubstituted example, yield only polymeric products. Applications must take cognizance of this limitation but otherwise the reaction appears quite feasible for demethylation and demethylenation of appropriately substituted catechol ethers. When compared with the more drastic and unselective hydrolytic methods, AgO oxidation is clearly a method to be considered.

Isolated methoxyl groups which do not possess an ortho or para methoxyl neighbor are not attacked by AgO;[6] however, a question of selectivity remains when several methoxyl groups arranged ortho and para with respect to each other are present in the same molecule. For example, a 1,3,4-trimethoxy arrangement allows investigation of competition between *o*- and *p*-quinone formation. The trimethyl ether of phthiocolhydroquinone, 2-methyl-1,3,4-trimethoxynaphthalene, a convenient model for the system, was oxidized by AgO to a mixture of two quinones, 2-methoxy-3-methyl-1,4-naphthoquinone and 4-methoxy-3-methyl-1,2-naphthoquinone. Orange-yellow needles, softening at 111°, of the *o*-quinone were obtained in 50% yield while the *p*-quinone was obtained in 40% yield in addition to a trace of phthiocol arising *via* hydrolysis. Such a competition though interesting is not unique, having been previously observed upon chromic acid oxidation of the dimethyl ether of dihydrolatifolin, a similarly substituted nucleus.[16]

Finally, in an example of relevance to quinone chemistry, a 1,2,3,4-tetramethoxy arrangement can upon oxidative demethylation provide an entry into the ubiquinone series if para oxidation is favored. Thus, 2,3-dimethoxy-5-methyl-1,4-benzoquinone (ubiquinone-0) was obtained in 64% yield from the action of AgO on 1-methyl-2,3,4,5-tetramethoxybenzene with concomitant production of several highly colored impurities which by analogy with the above reaction are ortho quinoid in nature.[17] Because of the instability of the *o*-quinones involved (two of the three possibilities have an open para position), further isolation was not attempted. Nevertheless, the desired direction of cleavage occurs to a significant enough extent to allow protection–deprotection of ubiquinones as methyl ethers so that these quinones too can be manipulated as their protected hydroquinones.

In summary, AgO appears to effect oxidative demethylation to quinones of a broad class of aromatic compounds bearing 1,2-dimethoxy or -methylenedioxy and 1,4-dimethoxy substituents. Oxidative side reactions have been shown to be minimal and thus the method is clearly superior to other reagents and should be applicable where these considerations are important. In addition, the method appears general for many quinones of biological interest, allowing the frequently impossible use of *O*-methyl protecting groups.

Experimental Section[18]

A. Preparation of Aryloxy Ethers. 2,3-Dimethyl-1,4-dimethoxynaphthalene. 2,3-Dimethyl-1,4-naphthoquinone[19] (2 g, 10.7 mmol) was reduced to the hydroquinone in ether solution with aqueous hydrosulfite. The ethereal solution was evaporated *in vacuo* in a round-bottomed flask; this flask was then sealed with a serum stopper and flushed with nitrogen, and 8 g of KOH in 16 ml of water was added. Dimethyl sulfate (10 g) was added to the contents (cooled to 0°), and the solution was allowed to stir for 1.5 hr during which time a light brown precipitate formed. This precipitate was filtered, washed with water, dried *in vacuo*, and sublimed at 60° (10 μ) to yield 2.1 g (90%) of 2,3-dimethyl-1,4-dimethoxynaphthalene. An analytical sample, recrystallized from

(13) R. Brockhaus, *Justus Liebigs Ann. Chem.*, **712**, 214 (1968).
(14) H.-J. Teuber and G. Staiger, *Chem. Ber.*, **88**, 802 (1955).
(15) M. Tomita and Y. Aoyagi, *Chem. Pharm. Bull.*, **16**, 523 (1968).
(16) D. Kumari, S. K. Mukerjee, and T. R. Seshadri, *Tetrahedron Lett.*, 3767 (1966).
(17) *o*-Quinones are also obtained in low yield upon nitric acid oxidation of melicopicine which contains a 1,2,3,4-tetramethoxy substituted nucleus; W. D. Crow, *Aust. J. Sci. Res., Ser. A*, **2**, 264 (1949).
(18) Nmr spectra were determined in $CDCl_3$ solution with a Varian T-60 instrument and are reported as δ values relative to internal TMS. Spectrophotometric measurements were made in isooctane using a Cary 14 recording spectrophotometer. Melting points are uncorrected. Elemental analyses were performed by the Analytical Laboratory, University of California, Berkeley, Calif. Column chromatographies were carried out on tlc grade Camag kieselgel while analytical tlc plates employed a 250-μ layer of kieselgel. Quantitative gc comparisons were accomplished with a 10 ft × 1/4 in. column containing 5% QF-1 liquid phase on 60–80 mesh acid-washed, DMCS-treated Chromosorb W. A CEC-130 mass spectrometer was used for ^{18}O analyses.
(19) M. F. Sartori, *Ann. Chim.*, **49**, 2157 (1957).

methanol–water, gave colorless prisms, melting at 74°: nmr δ 2.30 (s, $ArCH_3$), 3.80 (s, $ArOCH_3$), 7.3, 8.0 (m, ArH).

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.8; H, 7.5. Found: C, 77.8; H, 7.3.

2-Methyl-3-oxymethyl-1,4-dimethoxynaphthalene. 2-Methyl-3-formyl-1,4-dimethoxynaphthalene[3] (460 mg, 2 mmol) was dissolved in dry THF (4 ml), lithium aluminum hydride (40 mg, 1 mmol) suspended in dry THF (1 ml) was added slowly, and the solution was heated under reflux for 30 min. Addition of wet ether, filtering, and evaporating the filtrate afforded a crude product which was purified by chromatography (eluant, 40% ether–benzene) to yield 400 mg (90%) of 2-methyl-3-oxymethyl-1,4-dimethoxynaphthalene as colorless plates: mp 118–120°; nmr δ 2.40 (s, $ArCH_3$), 3.75, 3.83 (s, $ArOCH_3$), 4.73 (s, $ArCH_2O$–), 7.3, 7.8 (m, ArH).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.4; H, 6.9. Found: C, 72.2; H, 7.1.

4,5-Dimethyl-1,2-dimethoxybenzene. 4,5-Dimethyl-1,2-benzoquinone[14] (147 mg, 1.08 mmol) was reduced in chloroform solution with aqueous hydrosulfite. The crude catechol was dissolved under nitrogen in aqueous KOH (0.8 g in 1.6 ml of water), dimethyl sulfate (0.75 ml) was added, and the reaction mixture was stirred for 1 hr at room temperature. Crude product, obtained by extraction of the reaction mixture with ether, was chromatographed (eluant, 10% ether–petroleum ether) to give 4,5-dimethyl-1,2-dimethoxybenzene: mp 41–43° (lit.[20] mp 43–44°); yield, 107 mg (60%); nmr δ 2.13 (s, $ArCH_3$), 3.72 (s, $ArOCH_3$), 6.50 (s, ArH).

4,5-Dimethyl-1,2-methylenedioxybenzene. 4,5-Dimethyl-1,2-benzoquinone[14] (544 mg, 4.00 mmol) was reduced in chloroform solution with aqueous hydrosulfite. Crude catechol and anhydrous potassium carbonate (1.11 g, 8.00 mmol) were mixed in dry DMF (5 ml) under nitrogen, methylene bromide (833 mg, 4.80 mmol) was then added, the flask was sealed with a serum stopper, and the mixture was heated with stirring at 100° for 3 hr.[15] After cooling the reaction mixture, it was partitioned between petroleum ether and 1 *M* H_2SO_4. Crude product obtained from the petroleum ether layer gave 4,5-dimethyl-1,2-methylenedioxybenzene: mp 41–43° (lit.[21] 43–47°), in 22% yield after chromatography (eluant, 5% ether–petroleum ether); nmr δ 2.14 (s, $ArCH_3$), 5.78 (s, $-OCH_2O-$), 6.50 (s, ArH).

2-Methyl-1,3,4-trimethoxynaphthalene. Phthiocol (188 mg, 1.00 mmol) was reduced in ethereal solution with aqueous hydrosulfite. The hydroquinone was dissolved under nitrogen in aqueous KOH (1.6 g in 3.1 ml), dimethyl sulfate (1.45 ml) was added, and the reaction was stirred for 1 hr at room temperature. Crude product, obtained by petroleum ether extraction of the mixture, was purified by column chromatography to give 2-methyl-1,3,4-trimethoxynaphthalene[22] as a colorless oil: yield, 94 mg (43%); nmr 2.28 (s, $ArCH_3$), 3.74, 3.84 (s, $ArOCH_3$), 7.2, 7.9 (m, ArH).

1-Methyl-2,3,4,5-tetramethoxybenzene. 2,3-Dimethoxy-5-methyl-1,4-benzoquinone (ubiquinone-O)[23] (546 mg, 3 mmol) was reduced in ethereal solution with aqueous hydrosulfite. Crude hydroquinone was suspended in dimethyl sulfate (4.3 ml) and, with stirring under nitrogen, a solution of KOH (7 g) in water (14 ml) was added over 1 hr. The mixture was then heated on a steam bath for 30 min and the cooled reaction mixture was extracted with ether. The crude product so obtained was purified by chromatography (eluant, 15% ether–petroleum ether) to give 1-methyl-2,3,4,5-tetramethoxybenzene as a low melting, colorless oil (540 mg, 85%). Low-temperature (−50°) recrystallization from hexane was employed to obtain a sample melting at 50–52° (lit.[24] 51–52°): nmr δ 2.23 (s, $ArCH_3$), 3.78, 3.82 (s, 2,5-$ArOCH_3$), 3.88, 3.93 (s, 3,4-$ArOCH_3$), 6.45 (s, ArH).

1,4-Dimethoxynaphthalene,[25] 2-methyl-3-(3-methyl-2-butenyl)-1,4-dimethoxynaphthalene,[3] and 2-methyl-3-formyl-1,4-dimethoxynaphthalene[3] were prepared as described.

B. Oxidation of Aryloxy Ethers. Acidity Studies. 2,3-Dimethyl-1,4-dimethoxynaphthalene (43.2 mg, 0.200 mmol), AgO[26] (100 mg, 0.80 mmol), and dioxane (redistilled from sodium, 2 ml) were mixed in triplicate. Brief sonication formed a uniform dispersal of oxidant. The oxidations were then initiated by the addition of 3 *N* $HClO_4$ (0.4 ml), 6 *N* HNO_3 (0.2 ml), and 85% H_3PO_4 (0.2 ml) separately to each. The nitric and perchloric acid reactions were allowed to proceed until all AgO was consumed (*ca.* 2–3 min) while the phosphoric acid required 15 min with sonication during which time a grayish-white precipitate of Ag_3PO_4 formed. All three reactions were terminated by addition to $CHCl_3$–H_2O (8 ml/2 ml). After a second aqueous wash (2 ml), the chloroform extract was dried over anhydrous Na_2SO_4 and reduced in volume to 1.00 ml. For quantitative comparison a standard solution of 2,3-dimethyl-1,4-naphthoquinone (0.2 *M* in chloroform) was prepared. Aliquots (10 μl) of the reaction mixture and standard solution were then compared by gc to determine yields as shown in Table I. At a column temperature of 160°, starting material had a retention time of 12 min while the product quinone was obtained after 10 min. The sample which had been oxidized in the presence of phosphoric acid was chromatographed (eluant, 50% benzene–petroleum ether) to obtain 24 mg (65%) of pure 2,3-dimethyl-1,4-naphthoquinone: mp 127° (lit.[19] mp 126–127°); nmr δ 2.13 (s, $ArCH_3$), 7.7, 8.1 (m, ArH).

^{18}O Studies. $H_2{}^{18}O$-labeled 85% phosphoric acid was formed by adding $H_2{}^{18}O$ (0.38 ml, 21.3 mmol, 1.99% ^{18}O) slowly to P_2O_5 (620 mg, 4.34 mmol) in a stoppered flask at −80°. The frozen solution was warmed to room temperature and allowed to stand overnight to complete dissolution. The ^{18}O content of the water was then determined directly by mass spectrometry to be 1.70% ^{18}O (slight loss in label is ascribed to water absorbed by P_2O_5 during weighing). 2,3-Dimethyl-1,4-dimethoxynaphthalene was then oxidized on a 0.2-mmol scale with AgO and $H_2{}^{18}O \cdot H_3PO_4$. After purification as before, pure 2,3-dimethyl-1,4-naphthoquinone was obtained and pyrolyzed to carbon monoxide at 600° in a sealed tube; % ^{18}O = 1.65.[11] A control experiment was also performed in which 2,3-dimethyl-1,4-naphthoquinone was subjected to the reaction conditions, including AgO, for 5 min and recovered unchanged; ^{18}O = 0.28%. A sample of normal 2,3-dimethyl-1,4-naphthoquinone was also determined to have a 0.28% ^{18}O content by this analysis.

Oxidation of Hydroquinone Ethers. The various hydroquinone ethers were oxidized as described above under acidity studies employing nitric acid. The product quinones were identified by comparison with authentic samples where available and by uv and nmr absorption and gc and tlc.

2-Methyl-3-oxymethyl-1,4-naphthoquinone showed the following: mp 118–120°; nmr δ 2.27 (s, $ArCH_3$), 4.70 (s, $ArCH_2O$), 7.7, 8.1 (m, ArH); uv 330 (ε 2660), 265 (15,950), 258 (16,600), 248 (18,500), 243 nm (17,700).

Anal. Calcd for $C_{12}H_{10}O_3$: C, 71.3; H, 5.0. Found: C, 71.3; H, 4.8.

2-Methyl-3-formyl-1,4-naphthoquinone showed the following: mp 96–99°; nmr δ 2.44 (s, $ArCH_3$), 7.8, 8.1 (m, ArH), 10.60 (s, ArCHO); uv 335 (ε 2400), 258 nm (16,200).

Anal. Calcd for $C_{12}H_8O_3$: C, 72.0; H, 4.0. Found: C, 71.7; H, 4.1.

2-Methyl-1,3,4-trimethoxynaphthalene was oxidized with AgO and HNO_3 on a 0.3-mmol scale. Tlc (eluant, 10% ether–benzene) of the crude reaction mixture indicated two quinoid products, R_f 0.70 (yellow) and R_f 0.35 (orange). **2-Methoxy-3-methyl-1,4-naphthoquinone** corresponding to the less polar spot was obtained pure by chromatography; yield, 43 mg (40%). A sample recrystallized from hexane melted from 92 to 94° (lit.[22] mp 94°): nmr 2.08 (s, $ArCH_3$), 4.11 (s, $ArOCH_3$), 7.7, 8.1 (m, ArH); uv 327 (ε 2960), 272 (14,100), 248 (17,900), 244 nm (16,400).

4-Methoxy-3-methyl-1,2-naphthoquinone also was obtained from the chromatography (28 mg, 50%). An analytical sample recrystallized from chloroform–ether gave orange needles which softened at 111° and melted with loss of color at 145–147°: nmr δ 2.07 (s, $ArCH_3$), 4.03 (s, $ArOCH_3$), 7.6, 8.0 (m, ArH); uv 400 (ε 2460), 335 (1270), 323 (1400), 256 (29,900), 249 nm (29,800).

Anal. Calcd for $C_{12}H_{10}O_3$: C, 71.3; H, 5.0. Found: C, 70.9; H, 5.2.

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